REMARKS

The Office Action and the cited and applied references have been carefully studied. No claim is allowed. Claims 17-22, 24-33, and 35-37 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The examiner states that a reference to a prior application must be inserted as the first sentence of the specification of this application if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 120. Appropriate correction is required. This requirement is respectfully traversed.

The penultimate paragraph of MPEP 1893.03(c) states:

> Accordingly, it is not necessary for the applicant to amend the first sentence of the specification to reference the international application number that was used to identify the application during international processing of the application by the international authorities prior to commencement of the national stage under 35 U.S.C. 371.

Claims 17-37 have been rejected under 35 U.S.C. §112, first paragraph.

While the examiner agrees that a method for treating or preventing the rejection of renal allograft transplantation by administering a pharmaceutical composition comprising the chemokine receptor antagonist Met-RANTES and cyclosporin is

enabled as is a pharmaceutical comprising Met-RANTES and cyclosporin, the examiner holds that the scope of the claim as to "treating or preventing the rejection of transplanted organs, tissues or cells" and "a chemokine receptor antagonist" is not enabled. This part of the rejection is respectfully traversed.

Cyclosporin A is a commercially available drug which has attained widespread clinical application as an immunosuppressant in organ transplantation without any specificity towards any particular organ. A copy of the pertinent section in Martindale is attached hereto. Accordingly, cyclosporin can be used in general for treating or preventing the rejection of transplanted organs, tissues or cells by its immunosuppressive activity.

Met-RANTES has also recently been shown to give good results in animal models of intestine transplantation (Bedke et al., Met-RANTES improves acute-rejection-induced microvascular injury in rat small bowel transplantation, Transplant Proc. 34(3):1049 (2002); Stojanovic et al., Met-RANTES inhibition of mucosal perfusion failure in acute intestinal transplant rejection-role of endothelial cell-leukocyte interaction, J. Vasc. Res. 39(1):51-58 (2002)). Thus, both cyclosporin and Met-RANTES, as a preferred embodiment of a chemokine receptor antagonist, show activity in treating or preventing transplant rejection. Moreover,

Met-RANTES has the unexpected property of reducing the nephrotoxicity of cyclosporin (specification, page 6, first paragraph), which would be advantageous in all types of transplants treated with cyclosporin, not just renal transplants. Thus, even if the examiner continues to believe that Met-RANTES is not enabled for all types of transplants, despite evidence in the form of good results in renal and intestine transplants, then clearly the use of cyclosporin is enabled and Met-RANTES can simply be viewed as advantageously reducing cyclosporin nephrotoxicity when used in combination with cyclosporin.

With respect to the breadth of the chemokine receptor antagonist, the examiner states that there are many different chemokines and chemokine receptors and it is not clear that antagonizing receptors other than the RANTES receptors will have the desired effect. The examiner further states that the present invention would not be expected to work using any RANTES antagonist. This part of the rejection is respectfully traversed.

Met-Rantes is only one example of an antagonist of the chemokine receptors for RANTES. The present specification on page 6, lines 8-13, discloses other chemokine receptor antagonists of which truncated RANTES and N-terminally extended RANTES are among the other chemokine receptor antagonists reported in the cited references. Given the

guidance that the N-terminus can be modified, i.e., truncated or N-terminally extended, to produce RANTES antagonists and given the truncated or N-terminally extended RANTES already disclosed in the art, it would take only routine experimentation to find other antagonists of the chemokine receptors of RANTES.

Applicants also wish to point out that chemokines are among the most widely studied class of proteins and are known to be involved in a variety of diseases. There have been many successful attempts to design and produce chemokine receptor antagonists in order to produce drugs that can modulate the action of these molecules at sites of inflammation. Some modifications at the N-terminus for example are known to produce strong antagonists together with some mutations at putative GAG-binding domains. Therefore, it would not require undue experimentation to find other chemokine receptor antagonists that can be used according to the present invention.

Regarding "metabolites and synthetic analogs of cyclosporin", while applicants do not concede that they are not enabled by the present specification, applicants are canceling claims 23 and 34 merely to advance prosecution as part of their business strategy, thereby mooting this part of the rejection.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 17-19, 21-30, and 32-37 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Pattison et al., (1994) in view of Proudfoot et al. (1996) and further in view of Martindale. This rejection is respectfully traversed.

With due respect to the examiner, the examiner's conclusions appear to be a hindsight reconstruction of the present invention. Even if there were motivation to target RANTES for immunomodulation in transplant rejection and other immune-mediated diseases as asserted by the examiner, there is absolutely no suggestion or motivation whatsoever in any of the applied references to combine cyclosporin and a chemokine receptor antagonist, two separate immunosuppressive/ immunomodulating agents, to work synergistically together with the unexpectedly superior result that nephrotoxicity of cyclosporin is reduced in such a combination.

Although the examiner takes the position that a RANTES antagonist would prevent migration of T cells stimulated by RANTES and that cyclosporin would inhibit T cell proliferation, there can be no reasonable expectation that cyclosporin and a chemokine receptor antagonist would act synergistically, absent applicants' own results. Accordingly, there is simply no suggestion or motivation to one of ordinary skill in the art that cyclosporin and a chemokine receptor

antagonist would act synergistically with the added benefit of reducing cyclosporin nephrotoxicity.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 24 and 35 have been amended as follows:

24(Amended). The method according to claim ~~23~~ 17, wherein the cyclosporin is cyclosporin A.

35(Amended). The pharmaceutical composition according to claim ~~34~~ 30, wherein the cyclosporin is cyclosporin A.